Clinical & Experimental Immunology
The Journal of Translational Immunology

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/cei.12053

Specific antibody deficiency in children with recurrent respiratory infections: a controlled study with follow-up

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Accepted for publication 10 December 2012
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Summary

Specific antibody deficiency (SAD) to unconjugated pneumococcal vaccine (PPV) is an established primary B cell immunodeficiency. The occurrence and natural history of SAD in children is unclear. We conducted an observational study to identify SAD in children with recurrent respiratory infections. Ninety-nine children, mean age 5·9 (range 2–16) years, with recurrent or severe infections were vaccinated with PPV; serum antibody concentrations for serotypes 4, 6B, 9V, 14, 18C, 19F and 23F were measured before and 2 weeks after vaccination with enzyme immunoassay. The retrospective control group consisted of 89 healthy children matched for age and gender. No children had received previous conjugated pneumococcal vaccine (PCV) or PPV. The structured history of infectious diseases of all participants was collected. Ten of 91 (11%) children (eight excluded due to immunoglobulin G subclass deficiency) with recurrent respiratory infections had SAD. In the control group, three children (3%) responded inadequately to PPV ($P = 0{\cdot}05$). Most children with SAD also had many other minor immune defects. After 0·5–5 years (medium 3·8), eight children with SAD were revaccinated with PPV; five responded adequately and three inadequately. Two SAD children were revaccinated with PCV, one developed an adequate and one an inadequate response. Two children with SAD received treatment with intravenous immunoglobulin; the remaining eight children recovered without replacement therapy during the follow-up. SAD is common in young children with recurrent respiratory infections, but it is often transient and resolves itself within a few years without specific treatment.

Keywords: CVID, immunodeficiency, pneumococcal vaccine, recurrent infections, specific antibody deficiency

Introduction

Specific antibody deficiency (SAD) is an established primary B cell immunodeficiency which should be searched for in children aged ≥ 2 years with recurrent bacterial infections of the respiratory tract [1,2]. SAD is defined as an impaired specific immunoglobulin (Ig)G response to unconjugated pneumococcal polysaccharide vaccine (PPV) in subjects with normal serum concentrations of IgA, IgM, IgG and IgG subclasses. Usually, the responses to five to 14 vaccine serotypes are measured. Previously, an inadequate response was a post-vaccination concentration of <1·3 μg/ml or less than four times the prevaccination concentration in more than half of the serotypes tested [3,4]. Major problems are the wide variability of individual antibody responses, especially by age, and the variability of the immunogenic potential of the various serotypes [3,5]. It is not reliable for detecting this immunodeficiency in children <2 years of age, because in this age group the response to polysaccharide antigens may be physiologically impaired [6,7].

SAD is considered to be a relatively common primary immunodeficiency [2]. The prevalence is reportedly 7–19% among children with recurrent respiratory infections [4,8–13].

The natural history of SAD in children is unclear. It is not known if SAD in young children is a permanent immunodeficiency, a transitional phenomenon that resolves

spontaneously or whether it might progress to common variable immunodeficiency (CVID).

In this study, we searched for SAD in children with recurrent respiratory infections or severe infections and followed the children with SAD for 1–5 years. All children with impaired response were revaccinated. For comparison, we assessed also PPV responses in patients studied for diagnosis of CVID.

Methods

We conducted this observational follow-up study at the Department of Pediatrics, Turku University Hospital, Turku, Finland, from 1 January 2002 to 31 December 2010. The Turku University Hospital is the only tertiary-care hospital in southwestern Finland. It serves a population of about 750 000 and provides acute hospital care for approximately 69 000 children below 16 years of age. No referrals are received from outside the area.

Patients

In this study, the Infectious Disease Division evaluated and collected 99 children prospectively. The inclusion criteria were a recent history (given by the parents) of recurrent respiratory infections (clinical diagnosis of acute otitis media ≥5, sinusitis ≥3 and/or pneumonia ≥2) ($n = 91$) or a history of severe invasive infection ($n = 8$) and an age of 2–16 years at the time of evaluation (Table 1). No children had received previous PPV or PCV. The lifetime history of infections was collected using a standardized questionnaire. All children were vaccinated at the first visit, and assessment of the serotype-specific antibody response to PPV (Pneumovax 23; Merck, Rahway, NJ, USA) occurred before and 2 weeks after vaccination. In addition, total serum IgG, IgA, IgM levels, IgG subclass concentrations, the anti-tetanus toxoid IgG antibody level [14] and the function of the alternative, classical and lectin pathways of the complement system (COMPL 300 Wielisa Kit; Wieslab, Lund, Sweden) were assessed in all study participants. The number of C4A and C4B genes was studied in all patients with SAD with isotype-specific genomic real-time polymerase chain reaction amplification [15].

Patients with CVID

Twelve patients (four children and eight adults), other than in the study group, with low serum IgG, IgA and IgM concentrations were identified. They were vaccinated with PPV for the diagnosis of CVID during the study period. No one had received previous immunoglobulin treatment. Four of these patients were also vaccinated with tetanus toxoid and specific IgG responses to this vaccination were assessed [14].

The diagnosis of CVID included the decrease of two or more serum immunoglobulin isotype levels (IgG less than 2 standard deviations the age-adjusted mean), impaired antibody responses and exclusion of secondary hypogammaglobulinaemia.

Table 1. Study participants.

	Control group ($n = 89$)	Children with recurrent infection ($n = 91$)	Patients with IgG subclass deficiency ($n = 8$)	Patients with common variable immunodeficiency ($n = 12$)
Sex male : female	44:45	46:45	6:2	4:8
Age at time of pneumococcal immunization (years)				
2–4	25	26	0	1
5–10	47	47	3	0
11–15	14	13	4	3
>15	3	5	1	8
Mean (s.d.)	6·5 (3·7)	5·9 (3·8)	9·4 (3,4)	24·2 (18·2)
Asthma/allergy (%)	8 (9%)	42 (46%)	7 (87%)	0 (0%)
Number of acute otitis media cases during lifetime				
<5	63 (71%)	34 (37%)	5 (63%)	6 (50%)
5–10	14 (16%)	6 (7%)	0 (0%)	4 (33%)
≥10	12 (13%)	51 (56%)	3 (37%)	2 (17%)
Number of acute sinusitis cases				
<3	81 (91%)	57 (63%)	5 (63%)	1 (8%)
≥3	8 (9%)	34 (37%)	3 (37%)	11 (92%)
Number of pneumonia cases				
<2	87 (98%)	63 (69%)	4 (50%)	9 (75%)
≥2	2 (2%)	28 (31%)	4 (50%)	3 (25%)
Number of bacteraemia/sepsis cases	0 (0%)	6 (7%)	2 (25%)	3 (25%)

IgG: immunoglobulin G; s.d.: standard deviation.

Healthy children

Healthy children matched for age and gender ($n = 89$) served as a retrospective control group. No children had received previous PPV or PCV. They were vaccinated with PPV and serum antibody concentrations of seven pneumococcal serotypes were measured before and 2 weeks after vaccination. The history of infectious diseases of these children was collected using the same standardized questionnaire as for the children studied for suspected antibody deficiency (Table 1).

This study protocol was approved by the Ethics Committee of the Turku University Hospital.

Laboratory methods

Enzyme-linked immunosorbent assays (ELISAs) for IgG antibodies to pneumococcal serotypes and tetatus toxoid. All serum samples were analysed by the National Institute of Health and Welfare, Helsinki, Finland using an enzyme immunoassay using a 22F neutralization step [16]. The serotypes included were 4, 6B, 9V, 14, 18C, 19F and 23F. Anti-tetanus toxoid IgG antibodies were measured using the ELISA method as described by Salmi *et al.* [14].

Definition of specific antibody deficiency syndrome. SAD was defined as an inadequate response to more than four of the seven serotypes tested. An inadequate response to a given serotype was defined as a post-vaccination antibody concentration of <1·3 μg/l, or less than four times the prevaccination value [3,4].

Statistical methods

Comparisons between two dichotomous variables were performed using the χ^2 or Fisher's exact tests, as appropriate. The number of acute otitis media episodes was compared between the control group and the study group using the χ^2 test for trend. The Mann–Whitney *U*-test was used to compare the age of the children with and without an inadequate response to polysaccharide antigens. SAS for Windows version 9·2 was used for statistical analyses. *P*-values below 0·05 were considered statistically significant.

Results

SAD in children with recurrent respiratory infections

An inadequate IgG antibody response to PPV was found in 15 (15%) of 99 children with recurrent/severe infections. In the control group, three (3%) of 89 healthy children had an inadequate response ($P = 0{\cdot}01$). Eight of the 99 study children had an IgG subclass concentration below the age-matched reference range and they were analysed separately. Ten of 91 (11%) patients (eight cases of IgG subclass deficiency excluded) had SAD ($P = 0{\cdot}05$ when compared to the control group) (Table 2). Of these patients, eight had an inadequate response to four and two to five of the seven serotypes studied. When only a greater than twofold increase was used as a criterion, 13 of 91 of the study patients and four of 89 control children had inadequate responses ($P = 0{\cdot}02$).

The details of the antibody responses imply inconsistencies in the response criteria. The occurrence of impaired responses to polysaccharide antigens depended on the age of the children and was significantly ($P = 0{\cdot}02$) more common in young patients. The patient demographics are shown in Table 1. The children with recurrent infections had significantly more recurrent acute otitis media, sinusitis and pneumonia than the children in the control group ($P < 0{\cdot}001$ in all comparisons). Table 3 shows the clinical details of the 10 children with SAD. The mean age of SAD patients was 4 years; four patients were less than 3 years of age. The signs and symptoms of infections of most children had started within the first 6 months of life. Recurrent acute otitis media ($n = 6$), recurrent sinusitis ($n = 2$) or recurrent pneumonia ($n = 3$) were the most common illnesses. Only

Table 2. Specific immunoglobulin (Ig)G responses (μg/ml) before and 2 weeks after 23-valent unconjugated pneumococcal vaccine in 10 children with specific antibody deficiency (SAD); inadequate responses are shown in italic type.

No.	Age at dg, years	Serotype 4		Serotype 6B		Serotype 9V		Serotype 14		Serotype 18C		Serotype 19F		Serotype 23F	
		1	2	1	2	1	2	1	2	1	2	1	2	1	2
1	2·1	0·77	2·24	*0·43*	*0·67*	*0·35*	*1·13*	*1·08*	*1·29*	0·18	2·32	2·25	2·58	*0·43*	*0·63*
2	2·6	0·09	3·56	*0·05*	*0·05*	0·04	0·21	0·10	11·22	*0·12*	*0·44*	*1·60*	*0·62*	*0·04*	*0·04*
3	2·6	0·03	0·92	*0·07*	*0·16*	*0·11*	*0·22*	0·89	1·38	*0·11*	*0·36*	*0·67*	*1·00*	0·06	0·32
4	2·7	0·03	1·92	*0·05*	*0·05*	0·11	1·00	*0·10*	*0·10*	*0·34*	*0·53*	*0·08*	*0·08*	*0·04*	*0·04*
5	3·4	0·38	3·19	*0·25*	*0·48*	*0·53*	*0·82*	0·38	7·63	0·19	1·62	*0·56*	*1·20*	*0·16*	*0·45*
6	3·5	0·03	0·50	*0·09*	*0·13*	*0·14*	*0·32*	*0·54*	*0·64*	0·04	0·81	*0·34*	*1·11*	0·04	0·59
7	4·0	0·25	1·86	*0·41*	*0·40*	*0·39*	*0·91*	*0·38*	*0·65*	*0·39*	*1·12*	1·22	2·67	*0·21*	*0·38*
8	5·3	0·13	2·89	*0·20*	*0·46*	*0·49*	*0·61*	5·07	34·42	0·12	2·87	*0·73*	*1·16*	*0·22*	*0·59*
9	5·7	0·08	0·87	*0·23*	*0·25*	*0·36*	*0·56*	*0·10*	*0·10*	*0·14*	*0·69*	*0·40*	*0·84*	0·10	6·15
10	7·8	1·00	6·47	*0·29*	*0·45*	0·14	2·70	*0·35*	*0·54*	0·12	3·02	*0·53*	*0·67*	*0·14*	*0·24*

Table 3. Characteristics of 10 children with recurrent infections and specific antibody deficiency.

No	Sex	Age at dg (years)	Age at onset of infection (months)	Major illness before diagnosis (no.)				Allergy or asthma	Other immunodeficiencies	Follow-up after vaccination (years)	Infections during follow-up
				Pneumonia	AOM	Sinusitis	Other				
1	F	2·1	4	0	25	0	Chronic draining ear	No	One C4A gene	4·7	IVIG and prophylactic trimetoprim-sulpha for 6 months
2	F	2·6	2	3	20	0		No	IgA deficiency, lectin pathway 2%, no C4B genes	4·0	1 AOM, H1N1 influenza
3	F	2·6	5	5	3	0		Yes	No tetanus IgG	1·4	1 AOM, IVIG for 6 months
4	F	2·7	3	0	12	0	Recurrent folliculitis	No	Neutropenia, increased IgG4	5·6	8 AOM†
5	F	3·3	5	0	4	0	30 acute bronchiolitis, recurrent HSV infections	No	Neutropenia, lectin pathway 8%, one C4A gene	3·8	1 AOM, 1 bronchitis, 40 HSV infections
6	F	3·5	29	0	3	3	*S. pneumoniae* sepsis	Yes	One C4A gene	5·5	7 AOM†
7	M	4·0	3	0	20	3		Yes	No C4B genes, lectin pathway 15%, MBL 54 ng/ml	2·6	1 AOM
8	F	5·3	NK	3	0	0		Yes	One C4B gene	5·0	6 pneumonia, 15 bronchitis
9	F	5·7	3	1	30	0	Eosinophilic granuloma	Yes	One C4B gene	4·4	10 AOM, 3 tonsillitis, 10 laryngitis†
10	M	7·8	5	0	30	0	Chronic draining ear, 10 tympanostomy tubes	Yes	No C4B genes	1·1	3 AOM

†Revaccinated during follow-up. AOM: acute otitis media; HSV: herpes simplex virus; IVIG: intravenous immunoglobulin; MBL: mannose binding lectin; NK: not known; M: male; F: female.

one patient had had *Streptococcus pneumoniae* sepsis. According to parent reports, all children had received numerous antibiotic treatments (lifetime mean 30, range 15–50).

It is of note that most children with SAD also had other, minor defects in their immunity. Null alleles of complement C4A or C4B were detected in eight of 10 children, and of these eight children three had a defective complement lectin pathway. Co-existing neutropenia was present in two children. The IgG antibody responses to tetanus toxoid vaccinations were protective (>0·01 IU/ml) in nine of 10 children with SAD. One child had a non-detectable level of IgG antibodies after three tetanus toxoid vaccinations. Whether this child develops CVID in the future or will produce an antibody response to tetanus toxoid after revaccination is unclear.

Inadequate response to PPV in patients with IgG subclass deficiency and CVID

Four children had IgG2 deficiency (two of them had also IgG4 deficiency) and four had IgG3 deficiency. Five (63%) of these eight children had an inadequate response to PPV: three to four serotypes, one to five serotypes and one to six serotypes. One child with IgG3 deficiency had a positive response to all seven pneumococcal serotypes. Measurement of IgG antibodies to tetanus toxoid in seven children showed that their concentration was above the protective level in all cases.

Twelve patients with low serum IgG (mean 2·5 g/l, range 0·1–4·9 g/l), IgA and IgM concentrations and a history of recurrent sinusitis, acute otitis media, pneumonia or septicaemia before any immunoglobulin treatment were vaccinated. All 12 patients had an inadequate response to PPV: two patients to five serotypes, two patients to six and eight patients to seven. At the time of vaccination, IgG antibody levels to tetanus toxoid were measured in 10 patients. In all cases, they were above the protective level. Four patients were vaccinated with tetanus toxoid and three of them had an adequate antibody response (more than four times the prevaccination level).

Clinical follow-up and revaccination of children with SAD

The 10 children with SAD were followed for 1·1–5·6 (medium 3·8) years after vaccination with PPV and all infections were recorded during the follow-up. Intravenous Ig (IVIG) treatment and trimethoprim sulphamethoxazole prophylaxis for 6 months was initiated for two children (Table 3). The clinical response was positive in both cases, and the children remained healthy during and after treatment. At the follow-up visit, the parents of nine of 10 patients considered their children to be healthy or having a 'normal' number of respiratory infections during follow-up.

All 10 SAD patients received a second dose of pneumococcal vaccine after 0·5–5·5 years; eight were revaccinated with PPV and two with seven – valent PCV (Prevenar, Wyeth Lederle Vaccines, Brussels, Belgium). After revaccination with PPV an adequate response, as defined previously, occurred in five of eight patients; three patients had an inadequate response again; one of them had no changes in any serotype levels. One of the two children who were revaccinated with PCV developed an adequate response and one an inadequate response. Two children received a third dose of pneumococcal vaccine, one a second PPV after PPV followed by PCV and one a third PPV. Both children had adequate responses. Two children remained unresponsive and clinically healthy: one had an uneventful clinical course without treatment and one stayed healthy during and after IVIG treatment.

The three healthy children in the control group with an inadequate response were followed for 6 years. None had recurrent respiratory infections. One child was revaccinated with PPV 3·6 years after the initial vaccination and developed an adequate response.

Follow-up and revaccination of children with IgG subclass deficiency

During the 1–9 years of follow-up, the IgG subclass deficiency in eight children became normal in five. The IgG2 + IgG4 deficiency in two children was permanent; one of them was treated with IVIG and one was not. In one child, no follow-up samples were studied. All five children with IgG subclass deficiency and impaired responses to pneumococcal polysaccharide antigens responded normally to PCV 4 months to 5 years after the initial dose of PPV.

Discussion

We found SAD in 11% of the children with recurrent respiratory infections. This prevalence is in agreement with the results of previous studies [4,8–13,17]. In the control group, the prevalence of an inadequate response to PPV was 3%; in this respect, the difference between the group with recurrent infections and the control group was significant. Thus far, only one study shows an appropriate control group of healthy vaccinated children [12]. New observations are that immunodeficiency resolved spontaneously by clinical judgement in most children and that the laboratory values became normal within 1–5 years, suggesting that SAD in young children is often transient and probably constitutes simply a delay in the physiological maturation of response to polysaccharide antigens. It is well established that in infants both innate and adaptive immune responses are reduced. They fail to produce high levels of antibodies through several mechanisms in B cell responses, including B cell immaturity, signalling failure for B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), reduced levels of APRIL expression and reduced levels of expression of several receptors [18].

Most children in our study group showed warning signs of primary immunodeficiency: recurrent acute otitis media, recurrent sinusitis or recurrent pneumonia. Recently, a family history of infections was shown to be the only reliable warning sign of primary immunodeficiency [19]. In many children with SAD the laboratory diagnosis was often equivocal, and this made the reliability of the diagnosis questionable. Interestingly, impaired responses to six to seven of the seven serotypes studied were associated only with CVID (some with normal response to tetanus toxoid vaccination) and did not occur in children with SAD.

Only anecdotal data are available for the natural course and efficacy of IVIG treatment or antibiotic prophylaxis of children with SAD. Hidalgo *et al*. [17] identified five patients with SAD out of 78 children with recurrent infections. Three of these received IVIG replacement therapy and all responded favourably. Cheng and co-workers [20] reported 75 SAD patients aged 4–81 years. Thirty patients received IVIG therapy and the number of infections decreased significantly during treatment when compared to the number of infections before treatment. A recent survey by Yong *et al*. [21] showed that more than 80% of SAD patients are treated with IVIG in the United States. Of our eight untreated patients, all except one recovered during the follow-up, suggesting that IVIG treatment may not be necessary in most young children with SAD. Two of our eight patients with IgG subclass deficiency were treated with IVIG. One had an inadequate response to vaccination before treatment. IgG subclasses became normal in five of eight cases with subclass deficiency. These results are in agreement with earlier reports [1,22].

It is not known whether the children with SAD should be retested or immunized with PPV or PCV at some later time. Paris and Sorensen [23] state that patients aged 2–5 years may outgrow their immunodeficiency, and recommend revaccination 1–2 years after the initial vaccination. We revaccinated all our SAD patients with varying results: 1–5 years after the initial vaccination, all except two children had adequate antibody concentrations. One child, revaccinated with PPV 10 months after the initial vaccination, had no changes in the concentrations of antibodies in the pre- and post-vaccination sera. Of special note, in this context, is the observation that repeated doses of PPV may induce hyporesponsiveness, but the clinical implications of this type of hyporesponsiveness are unclear [24]. Pneumococcal conjugate vaccine can induce adequate IgG responses in children with SAD and all children with inadequate responses to PPV should be vaccinated with PCV [25]. In some centres, both PCV and PPV are given together when evaluating PPV response [26].

In the routine clinical work-up of our patients with recurrent respiratory infections, we also looked for other immunological defects. Interestingly, most children had

other minor immune defects such as neutropenia, C4A or C4B deficiency or decreased activity of complement lectin pathway. These common and subtle immunodeficiencies may have increased their susceptibility to recurrent infections. Bossuyt and colleagues [12] found an impaired antibody response to pneumococcal polysaccharides in seven (19%) of 55 children aged 4–14 years who had an increased susceptibility to respiratory infections, but in none of 37 control subjects. Deficiencies in the concentration of IgA and/or IgG subclasses, Gm(n) allotype and mannose-binding lectin 2 (MBL2) genotype were susceptibility factors. A combination of at least two susceptibility factors was present in 56% of the children. Emonts *et al.* [27] studied 348 children with recurrent otitis media and reported that PAI-1 4G/4G genotype, polymorphisms in the immunoresponse genes tumour necrosis factor (TNF)-α, interleukin (IL)-6, Toll-like receptor (TLR)-4 and IL-10 were associated with recurrent otitis media.

Several limitations of our retrospective study should be acknowledged. The weakness of all other SAD studies is the definition of what really constitutes an adequate or deficient response to each serotype tested. A recent report suggests that children aged 2–5 years should respond to 50% or more of the serotypes, with at least a twofold increase in titre and protective levels $\geq 1{\cdot}3$ μg/ml [26,28]. In this study, measurement of post-immunization responses occurred in the study group and in the control group at 2 weeks, while the 3–4-week interval was used in many other studies. However, adequate serotype-specific responses have been reported 2 weeks after immunization in infants aged 12 months [7]. Furthermore, in adults, final concentrations of pneumococcal antibodies peak by day 14 after vaccination [29]. In addition, in our study the number of the patients was small, although we studied children with recurrent infections for 9 years. A total of only 120 children with SAD appear in nine previous studies [4,8–13,17,25], although more than 2000 patients have been indentified worldwide [30]. Our study was observational, although we had a matched retrospective control group of healthy children. It must be stressed that in the healthy children's control group, one-third had suffered more than five episodes of acute otitis media, which may have affected our observations. Four of our 10 SAD patients were below 3 years of age and may have had impaired immunological defence only because of the immaturity of their immunological system. Our observations do not answer the question of whether or not young children with SAD should be treated with IVIG. The decision must be made preferentially on clinical grounds. We should have studied more serotypes. This will be possible in the future, when multiplex bead-based assays will be more readily available [13].

In conclusion, with the present diagnostic criteria, SAD is more common in children with recurrent infections than in healthy children. The pneumococcal serotypes used to detect SAD should be reconciled internationally, and reference values for antibody responses to different serotypes need to be defined for different groups [11]. Nevertheless, it is pertinent to question how useful is the information gained from anti-pneumococcal antibody measurement in young children. Combined with current knowledge, our observations suggest that the yield is poor when diagnosing SAD. In most young children, SAD is a transient delay of immunological maturation and resembles, in this sense, transient hypogammaglobulinaemia in infancy and most IgG subclass deficiencies. In young children, SAD may not be the same disease entity as SAD in adults. The diagnosis of SAD may have treatment implications for only a few patients. Conversely, concerning the diagnosis of CVID, polysaccharide antibody responses were highly valuable.

Acknowledgements

We thank Kaisu Kaistinen RN for her assistance in the conduct of the study and Jaakko Matomäki MSci for statistical help. This study was supported by grants from the government of Finland to the Turku University Hospital.

Disclosure

None.

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